REMARKS

Claims 5, 7-9, 26-27, 29, 31, 37, 48-51, 56, 58, 70, 72, 76, 78, 108, 110, 117, 127-129, 131-135, 137, 147, 150, 156, 158-159, and 161-169 were pending in the present application, prior to Amendment. Claims 56, 110, 135, 137, 147, 150 and 162-163 were previously withdrawn from consideration, but in the Non-Final Office Action dated 2/8/11, the Examiner included claims 56 and 10 in the elected group and examined these claims. Applicants note that, in accordance with MPEP 821.04(b), Applicants will be entitled to rejoinder of process claims that depend from and include all the limitations of an allowable product claim.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order in which they appear in the Office Action.

35 U.S.C. §112, Written Description

The Examiner has rejected claims 1, 5, 7-9, 26, 29, 31, 37, 48-51, 56, 58, 70, 72, 76, 78, 108, 110, 117, 127-129, 131-134, 156, 158, 159, 161, 164-167, 168 , and 169 under 35 U.S.C. §112, first paragraph. The Examiner alleges that claims 1, 168, and 169 introduce new matter in reciting "the polypeptide is not fibrin" and "with the proviso that the protease domain is not urokinase plasminogen activator," because the specification and claims as originally filed allegedly do not disclose these exclusions as preferred embodiments of the claimed invention.

Applicants respectfully traverse, and wish to clarify the scope of the pending claims. Applicants point out that claim 1 is not currently pending. Applicants respectfully point out that the specification contains support for both fibrin and urokinase plasminogen activator. Fibrin is disclosed in the specification as one of many potential polypeptide substrates for proteolytic cleavage. Table 1 discloses fibrin, as does paragraph [0215], which states that "additional examples of cell surface associated or extracellular matrix targets for the subject adzymes include...fibrin..." Urokinase plasminogen activator (also abbreviated uPA and called urokinase) is disclosed in paragraph [0321], which lists "certain preferred embodiments, [in which] proteases that are useful as

catalytic moieties in the present invention are set forth." Applicants may freely choose to omit specific species, including fibrin and urokinase plasminogen activator, from the bounds of protection sought. According to *In re Johnson*, 558 F. 2D 1008 (CCPA 1977), a specification which discloses species also provides more than ample basis for claims reciting a limited genus in which the species have been excluded.

Applicants respectfully request reconsideration and withdrawal of the rejection.

35 U.S.C. §102

Applicants note with appreciation that the Examiner has withdrawn the rejection of claims 5, 7-9, 37, 48-51, 58, 70, 72, 74, 76, 78, 108, 127-129, 156, 157-58, and 164-165 under 35 U.S.C. §102 as being anticipated by Holvoet et al. (JBC 1991, vol. 266, pp 19717-9724, hereinafter "Holvoet").

35 U.S.C. §103(a)

The Examiner has rejected claims 5, 7-9, 37, 70, 73, 76, 78, 108, 117, 127-129, 156, and 164-165 under 35 U.S.C. §103(a) in view of Davis et al. (WO 00/64485, hereinafter "Davis") and Bhatia et al., (Int'l J. Cancer 2000, 85, 571, hereinafter "Bhatia"). Allegedly, Davis teaches fusion proteins and Bhatia teaches antibody-targeted enzymes made by a gene fusion method. The Examiner reasons that "one knowledgeable in prior art is motivated to make the protein conjugate of Davis by gene fusion methodology as taught by Bhatia" (page 5 of the Office Action), and one would use the resulting adzyme to inactivate substrate polypeptides by catalyzing the proteolytic cleavage of the substrate polypeptide.

The Examiner includes claims 70, 72, 76, and 78 in the rejections, because Davis allegedly teaches that substrates can be receptors, signaling molecules like cytokines, EGF-like factors, etc. In addition, claim 165 is rejected because the claim allegedly requires a substrate polypeptide from a specific target such as a protein aggregate, or a specific protease such as metalloproteinase, which elements are allegedly taught by Davis.

Applicants respectfully traverse. In the Office Action, the Examiner has provided a broad characterization of Davis and Bhatia and attempted to combine general elements of these references to arrive at the pending claims. However, Applicants submit that the proposed combination does not fulfill the criteria for establishing a *prima facie* case of obviousness: (1) suggestion or motivation to combine the references, (2) reasonable expectation of success, and (3) consideration of all claim limitations (MPEP 2143). As a first point, one of skill would not be motivated to combine Davis and Bhatia, based on a close reading of the specific teachings of the references. Starting with Davis, the reference discloses enzymes, such as chymotrypsin or matrix metalloproteinase (MMP), which are joined by chemical conjugation to a targeting molecule such as a chemical ligand or a protein. Davis states that "preferred chimeric molecules of this invention are chemically coupled molecules rather than fusion proteins" (page 20, lines 28-30), and "[i]n preferred embodiments, the chimerical catalytic antagonists and/or redirected enzymes of this invention are made by chemically conjugating the desired enzyme…to the targeting moiety" (page 40, section entitled "Construction of chimeric molecules," lines 29-31). Davis particularly emphasizes the benefits of using chemical conjugation, because chemical coupling imparts flexibility in the design and testing of the molecules, and further, facilitates the use of targeting domains that may be small organic molecules or other non-protein ligands. Davis also enumerates many advantages for using non-protein targeting moieties (see, for example, page 20, line 31 to page 21, line 12), and provides specific teaching for modifying enzymes to make them suitable for chemical conjugation. Given this emphasis, it is unlikely that one of skill would alter the teachings of Davis to make fusion proteins rather than chemical conjugates. In fact, Davis teaches away from making fusion proteins because such fusions (i) would lack the benefits described by Davis for chemical conjugates and (ii) would be unsuitable for use in the context of non-protein targeting moieties. Thus, one of skill would not turn to other references, such as Bhatia, for guidance in making fusion proteins, because one would not be motivated to ignore the chemical cross-linking method encouraged by Davis. Doing so would alter the principle of operation of Davis. According to MPEP 2143.01: "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references

are not sufficient to render the claims prima facie obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (C.C.P.A., 1959)."

Conversely, one of skill reading Bhatia would not be motivated to introduce elements from Davis to arrive at the present claims. Bhatia discloses one specific fusion protein made up of a bacterial enzyme CPG2 and an antibody that binds to the tumor-specific molecule carcinoembryonic antibody (CEA). This fusion protein delivers CPG2 to tumors, where CPG2 converts prodrugs into cytotoxic agents at the site of the tumor mass. Bhatia terms this process antibody-directed enzyme prodrug therapy (ADEPT), and describes how one specific fusion protein, whose component parts were carefully designed, confers advantages over other fusion proteins in ADEPT for CEA-expressing tumors. Bhatia does not teach or suggest modifying the fusion protein, for example, by altering the ligands, enzymes, or the conjugation between the two. Indeed, any deviance from the specific fusion protein of Bhatia could not be expected to produce the same satisfactory and superior results that Bhatia describes. Substituting the enzymes of Davis, as suggested by the Examiner, would require replacing CPG2 with chymotrypsin or MMP, which would destroy the ability of the fusion protein to convert a pro-drug to a cytotoxic agent at the site of the tumor mass. Because this change would render the fusion protein of Bhatia "unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." *In re Gordon*, 733 F. 2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Accordingly, one of skill would not combine Davis and Bhatia to arrive at any of claims 5, 7-9, 37, 70, 72, 73, 76, 78, 108, 117, 127-129, 156, and 164-165. Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim 48 is rejected under 35 U.S.C. §103(a) as being unpatentable over Davis in view of Bhatia and futher in view of Tamburini (US Patent No. 5,981,208, hereinafter "Tamburini"). Allegedly, Tamburini teaches the use of secretase to catalyze the proteolytic cleavage of amyloid precursor protein in an amyloid deposit, and it would have been obvious to make a fusion protein comprising secretase conjugated to an antibody molecule as taught by Davis and Bhatia. Applicants respectfully traverse. As discussed above, one of skill would lack motivation to combine Davis and

Bhatia, because doing so would require one of skill to change the principle of operation disclosed by Davis and/or render the fusion protein of Bhatia unsuitable for its intended purpose. Tamburini does not remedy this defect. Tamburini discloses methods for diagnosing Alzheimer's Disease (AD), comprising mixing cerebrospinal fluid (CSF) from patients with an amyloid precursor protein (APP) substrate. The assay relies on activity of endogenous proteases found in the CSF, and does not use a purified enzyme or an engineered molecule like the claimed adzymes. Thus, Applicants submit that Tamburini does not provide any motivation to combine the teachings of Davis and Bhatia, and further, does not supply any missing elements that could be combined with either or both references to arrive at the adzymes of the pending claims. Moreover, if an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is also nonobvious (*In re Fine*, 837 F. 2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Applicants request further clarification of the rejection, and/or reconsideration and withdrawal of the rejection.

Claim 58 is rejected under 35 U.S.C. §103(a) as being unpatentable over Davis in view of Bhatia and further in view of Dolinar et al. (Food technol and biotech. 2000, 38:5-9, hereinafter "Dolinar"). Allegedly, Dolinar teach methyl methane-thiosulfonate (MMTS), a reversible protease inhibitor in the purification and refolding of a cysteine protease type protein, and one of skill in the art would allegedly be motivated to purify a fusion protein complex of Davis using a protease inhibitor. Applicants respectfully traverse. As discussed above, one of skill would lack motivation to combine Davis and Bhatia, because doing so would require one of skill to change the principle of operation disclosed by Davis and/or render the fusion protein of Bhatia unsuitable for its intended purpose. Dolinar does not remedy this defect. Dolinar's disclosure of a proteinase inhibitor does not provide any motivation to combine the teachings of Davis and Bhatia, and does not supply any missing elements that could be combined with either or both references to arrive at the adzymes of the pending claim. Moreover, if an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is also nonobvious (*In re Fine*, 837 F. 2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Applicants request reconsideration and withdrawal of the rejection.

Claims 49-50, and 158 are rejected under 35 U.S.C. §103(a) as being unpatentable over Davis in view of Bhatia and further in view of Steinhauer et al. (Virology, 1999, 258, pp 1-20, hereinafter "Steinhauer"). Allegedly, it would have been obvious to one of skill in the art to make a fusion protein comprising a protease conjugated to an influenza virus specific antibody molecule, as taught by Davis and Bhatia, because Steinhauer allegedly teaches that activated hemagglutinin is essential for infectivity of the influenza virus. Applicants respectfully traverse. As discussed above, one of skill would lack motivation to combine Davis and Bhatia, because doing so would require one of skill to change the principle of operation disclosed by Davis and/or render the fusion protein of Bhatia unsuitable for its intended purpose. Steinhauer does not remedy this deficiency. Steinhauer primarily discloses protease-mediated activation of hemagglutinin, and does not teach or suggest proteolytic degradation of activated hemagglutinin, much less degradation mediated by an influenza-specific antibody. Thus, Steinhauer fails to provide motivation to combine the teachings of Davis and Bhatia, and does not supply any missing elements that could be combined with either or both references to arrive at the adzymes of the pending claims. Moreover, if an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is also nonobvious (*In re Fine*, 837 F. 2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Applicants request further clarification of the rejection, and/or reconsideration and withdrawal of the rejection.

Claims 56, 110, and 167 are rejected under under 35 U.S.C. §103(a) as being unpatentable over Davis in view of Bhatia and further in view of Schooltink et al. (J. Interferon and Cytokine Res., 2002, 5, 505-516, hereinafter "Schooltink"). Allegedly, it would have been obvious to one of skill in the art to make a fusion protein of Davis and Bhatia to inactivate substrate polypeptides in TNF-alpha because Schooltink allegedly teaches the importance of TNF-alpha receptors in inflammatory diseases and drug development. Applicants respectfully traverse. As discussed above, one of skill would lack motivation to combine Davis and Bhatia, because doing so would require one of skill to change the principle of operation disclosed by Davis and/or render the fusion protein of Bhatia unsuitable for its intended purpose. Schooltink does not remedy this deficiency. Schooltink provides a review of cytokines, but this disclosure does not provide any motivation to combine the teachings of Davis and Bhatia, and does not supply any missing elements that could be

combined with either or both references to arrive at the adzymes of the pending claim. Moreover, if an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is also nonobvious (*In re Fine*, 837 F. 2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Applicants request further clarification of the rejection, and/or reconsideration and withdrawal of the rejection.

Claims 26, 29, 31, 159, 161, and 165-166 are rejected under 35 U.S.C. §103(a) as being unpatentable over Davis in view of Bhatia and further in view of Guo et al. (Biotech. and Bioeng. 2000, 70, 456-463, hereinafter "Guo"). Allegedly, it would have been obvious to make a fusion protein as taught by Davis by fusing a serine protease via a linker as taught by Guo, because Guo allegedly teaches the advantages of using $(Gly_4Ser)_3$ as a linker. As discussed above, one of skill would lack motivation to combine Davis and Bhatia, because doing so would require one of skill to change the principle of operation disclosed by Davis and/or render the fusion protein of Bhatia unsuitable for its intended purpose. Guo does not remedy this deficiency. Guo describes a fusion protein comprising L-asparaginase (ASNase), a $(Gly_4Ser)_3$ linker, and protective scFv, but the disclosure of the linker and the use of a different antibody does not provide any motivation to combine the teachings of Davis and Bhatia, and does not supply any missing elements that could be combined with either or both references to arrive at the adzymes of the pending claim. Moreover, if an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is also nonobvious (*In re Fine*, 837 F. 2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Applicants request further clarification of the rejection, and/or reconsideration and withdrawal of the rejection.

Claim 51 is rejected under 35 U.S.C. §103(a) as being unpatentable over Davis in view of Bhatia and further in view of Debburman et al. (PNAS 1997, 94, 13938-13943, hereinafter "Debburman"). Allegedly, it would have been obvious to make a fusion protein comprising a protease conjugated to a prion specific antibody according to the method taught by Davis and Bhatia. The Examiner argues that Debburman teaches two forms of prion proteins, a protease labile form and a protease resistant form, and a fusion protein would bind to a prion molecule and degrade it before it turns into the resistant form. Applicants respectfully traverse. As discussed above, one of skill would lack motivation to combine Davis and Bhatia, because doing so would require one of

skill to change the principle of operation disclosed by Davis and/or render the fusion protein of Bhatia unsuitable for its intended purpose. Debburman does not remedy this deficiency. Debburman describes a role of molecular chaperones in converting prion proteins to an abnormal conformation. However, this reference does not provide any motivation to combine the teachings of Davis and Bhatia, and does not supply any missing elements that could be combined with either or both references to arrive at the adzymes of the pending claim. Moreover, if an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is also nonobvious (*In re Fine*, 837 F. 2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Applicants request further clarification of the rejection, and/or reconsideration and withdrawal of the rejection.

Claims 131-134 are rejected under 35 U.S.C. §103(a) as being unpatentable over Davis in view of Bhatia and further in view of Sanderson et al. (Medic. Res. Rev. 1999, hereinafter "Sanderson"). Allegedly, Sanderson teach a reversible, small molecule protease inhibitor that is used with a pharmaceutical composition. The Examiner argues that it would have been obvious to make a pharmaceutical preparation comprising a fusion protein as taught by Davis and Bhatia, and combine it with a reversible protease inhibitor as taught by Sanderson. Applicants respectfully traverse. As discussed above, one of skill would lack motivation to combine Davis and Bhatia, because doing so would require one of skill to change the principle of operation disclosed by Davis and/or render the fusion protein of Bhatia unsuitable for its intended purpose. Sanderson does not remedy this deficiency. Sanderson describes noncovalent inhibitors for thrombin and Factor Xa, but this disclosure does not provide any motivation to combine the teachings of Davis and Bhatia, and does not supply any missing elements that could be combined with either or both references to arrive at the adzymes of the pending claim. Moreover, if an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is also nonobvious (*In re Fine*, 837 F. 2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Applicants request further clarification of the rejection, and/or reconsideration and withdrawal of the rejection.

Double Patenting

The Examiner maintains the provisional rejection of claims 5, 7-9, 26-27, 29, 31, 35, 37, 52-53, 58, 69-70, 72, 74, 76, 78, 108, 119, 127-129, and 131-134 under the judicially created doctrine of obviousness type double patenting over claims 1, 4-5, 19-27, 30-34, and 37-41 of co pending Application No. 10/792,498 and 10/650,591.

Applicants reiterate that if conflicting claims are first allowed in these two copending U.S. Applications, Applicants note that, pursuant to 37 C.F.R. §1.130(b), a timely filed terminal disclaimer in compliance with 37 C.F.R. §1.321(c) may be used to overcome the double patenting rejection. In the meantime, and given that there has been no indication of allowable subject matter in the instant application, Applicants ask that this rejection be held in abeyance until indication of allowable subject matter. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

Applicants note that, in accordance with MPEP 804.I.B., the Examiner will maintain the provisional double patenting rejection until there are either no longer any conflicting claims or the double patenting rejection is the only remaining rejection in at least one of the applications.

Co-Pending Applications

The following co-pending, commonly-assigned applications were previously brought the Examiner's attention: Application No. 10/650,951, and 10/792,498. The Examiner is again invited to consider all past, present, and future prosecution in these co-pending applications.

CONCLUSION

In view of the foregoing remarks, Applicants believe the pending application is in condition for allowance.

Applicants believe no fee is due with this response other than those specifically authorized in connection with this submission. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. COTH-P01-001 from which the undersigned is authorized to draw.

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Respectfully submitted,

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